Case 4-18634/A/CCN

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE US PATENT APPLICATION OF
YIQING ZOU ET AL.
SERIAL NO. 08/216,440
FILED: March 23, 1994
FOR: ANTIMALARIAL COMPOSITIONS

Commissioner of Patents and Trademarks
Washington D.C. 20231 USA

DECLARATION OF WALTHER H. WERNSDORFER UNDER RULE 132

I, Walther H. Wernsdorfer, citizen of the Federal Republic of Germany and resident of Vienna, Austria, do hereby declare and say as follows:

That I am a Graduate of The Friedrich Alexander University of Erlangen, Federal Republic of Germany, where I graduated in 1952 and obtained the approbation in medicine (M.B.B.S);

That I am a Graduate of The Ludwig Maximilian University of Munich, Federal Republic of Germany, where I graduated in 1953 and obtained the Degree of a Doctor of Medicine (M.D.);

That I have undergone postgraduate training in tropical medicine at the Swiss Tropical Institute in Basel, Switzerland, and obtained in 1952 the Diploma of Tropical Medicine (D.T.M.);

That I have undergone postgraduate training in public health at the University of Bristol, U.K., and obtained in 1967 the Diploma of Public Health (D.P.H.);

That, as from 1958 until 1988, I have served the World Health Organization as a staff member in the fields of tropical medicine and malaria; between 1978 and 1988 as Chief Medical Officer in charge of global malaria research and *ex officio* Secretary of the Scientific Working Groups on the Chemotherapy and Immunology of Malaria, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases;

That, as from 1960, I held academic teaching assignments in addition to my WHO assignments, with the Faculty of Medicine, University of Khartoum, Sudan, the University of Tunisia, and the Université Claude Bernard, Lyon, France;

That, in 1988, I have been appointed visiting professor at the University of Vienna, Austria, and the Universiti Sains Malaysia, Penang, and in 1993 at the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand;

That I am the principal author or coauthor of approximately 100 publications, mainly in the field of malaria and malaria chemotherapy;

That I am a registered member of the medical profession (Medical Board of Central Franconia, Federal Republic of Germany);

That I am a member of the following professional bodies/organizations:

World Health Organization (WHO) Expert Panel on Malaria
German Society of Tropical Medicine (Honorary Member)
Swiss Society of Tropical Medicine and Parasitology (Honorary Member)
Austrian Society of Tropical Medicine and Parasitology (Council Member)
Royal Society of Tropical Medicine and Hygiene (U.K.)
British Society of Public Health
British Society of Parasitology;

That I am presently working as Visiting Professor (Tropical Medicine) at the Institute for Specific Prophylaxis and Tropical Medicine, Faculty of Medicine, University of Vienna, Austria, and Visiting Professor at the National Centre for Drug Research, Universiti Sains Malaysia, Penang, Malaysia (Tropical Clinical Pharmacology), and as Visiting Professor at the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (Tropical Clinical Pharmacology);

That I am the editor of the standard textbook entitled ***Malaria. Principles and Practice of Malariology*** (ISBN 0 443 024170) with Sir Ian McGregor being the coeditor;

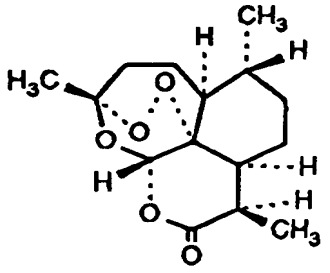
That this textbook was first published in 1988 in two volumes by Churchill Livingstone (Edinburgh, London, Melbourne and New York);

That I am the author of Chapter 51 (Exhibit 1): Recent progress of malaria research: chemotherapy, pages 1569-1674, with P.I.Trigg being the coauthor;

That this chapter and the references cited therein define the complete state of the art in 1988 with regards to the natural product qinghaosu (artemisinin) and the derivatives synthesized therefrom, and also define the relevant state of the art at the first U.S. filing date of Ser.No. 07/714,229, filed June 12, 1991;

That the following statements and the conclusion drawn therefrom agree with the contents of this Chapter 51 from the textbook;

That at this first U.S. filing date the antimalarial activity against *Plasmodium falciparum* of the natural antimalarial product qinghaosu (=artemisinin), isolated from the indigenous plant Qinghao (*Artemisia annua* L.), was established in various *in-vitro* and *in-vivo* experimental models and in clinical trials involving patients with naturally acquired malaria:

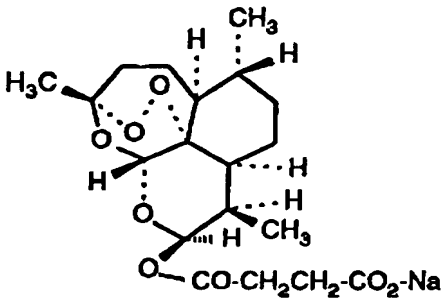
I:  (qinghaosu, artemisinin),

That the reason for preparing structural derivatives of qinghaosu appears its insufficient ability to effect complete parasite clearance, which has been established in clinical trials in which this natural product was tested by administering different dosage forms such as tablets, capsules or intramuscular injections, thus rendering qinghaosu unsatisfactory for the radical treatment of malaria;

That the unsatisfactory curative effect of qinghaosu was ascribed to its poor solubility in water and injectible carriers precluding the establishment of adequate concentrations in the blood;

Water soluble artemisinin derivative

That at this first U.S. filing date, the following structural derivatives of artemisinin (Ia, Ib) had been selected for inclusion in pharmaceutical dosage forms suitable for human administration:

Ia:  (Na-artesunate, i.v.,i.m., water solution);

That Na-artesunate is characterized by a grossly improved water solubility as compared to qinghaosu;

That Na-artesunate is higly unstable in water, leading by hydrolysis within less than one hour to a nearly complete transformation to dihydro-artemisinin and Na-succinate;

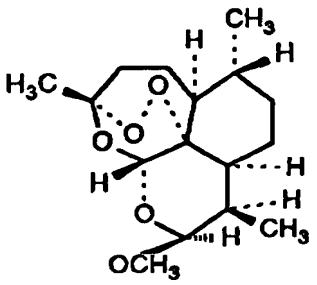
That the improved water solubility of Na-artesunate is attributed to a higher degree of hydrophility as compared to qinghaosu resulting from the substitution of the qinghaosu structure with the hydrophilic Na-succinyl group;

That the improved water solubility of Na-artesunate and subsequent formation of dihydro-artemisinin resulted in an increased antimalarial activity upon oral administration as compared to artemisinin due to increased absorption in the gastro-intestinal tract;

That due to this increased gastro-intestinal absorption Na-artesunate appeared suitable for oral administration;

That due to the low stability in aqueous suspension and its hydrolysis product dihydroartemisinin, as unanimously reported in various references, Na-artesunate appeared unsuitable for formulation in an oral dosage form with a stability acceptable to regulatory authorities;

Water insoluble artemisinin derivative

Ib:  (artemether, i.m., oily solution);

That artemether is characterized by an extremely low water solubility similar to qinghaosu but satisfactory solubility in unpolar carrier liquids such as oils;

That the low water solubility and the hydrophobic character of artemether is self-evident from the absence of a hydrophilic group in the structure;

That due to the solubility of artemether in organic carrier liquids such as oils this hydrophobic derivative appeared particularly suitable for the preparation of intramuscular dosage forms containing pharmaceutically acceptable oils as carrier liquids;

That the absorption of artemether from the gastro-intestinal tract was *a priori* thought to be poor due to the relatively high stability and the hydrophobic character of this natural product;

That the oral route of administration of the individual agent artemether was deemed blocked until 1992 as clearly stated by J.Karbwang et al., The Lancet, Vol. 340, Nov. 21, 1992 (1245-1247): Comparison of oral artemether and mefloquine in acute uncomplicated falciparum malaria (Exhibit 2):

Artemether is an effective antimalarial drug with a rapid onset of action that destroys asexual parasites at an early stage of development. The potency of this drug has been shown in clinical trials in China and Burma (references omitted). Artemether clears parasites rapidly with virtually no side-effects. Artemether is, however, associated with a high rate of recrudescence that varies with duration of treatment and the total dose given. The recommended dose of artemether has been 600 mg given over 5 days, but we have found the cure rate to be only 90 % with intramuscular artemether at this dose (reference omitted). There are no reports on the efficacy of oral artemether in multiple-drug resistant falciparum malaria, and the proper dosage regimen of artemether for the treatment of this condition remains to be decided...

Conclusion

That at the first U.S. filing date a qinghaosu derivative meeting both essential requirements of acceptable stability and solubility was not available for oral administration;

That at the first U.S. filing date the suitability of artemether for inclusion in solid oral dosage forms was not known;

That at the first U.S. filing date the antimalarial effect of a solid oral dosage form containing the combined agents artemether and benflumetol was unpredictable;

That it was unpredictable from the literature that the combination of benflumetol with artemether in the combined oral dosage form would render the insoluble compound artemether water soluble or absorbable in the gastro-intestinal tract;

That it was also unpredictable that a combined dosage form would increase the solubility or the gastro-intestinal absorption of the component artemether;

The Undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issueing thereon.

The following exhibits are part of the Declaration:

1. ***Malaria. Principles and Practice of Malariology***, Chapter 51: Recent progress of malaria research: chemotherapy, pages 1569-1674.

2. J.Karbwang et al., The Lancet, Vol. 340, Nov. 21, 1992 (1245-1247): Comparison of oral artemether and mefloquine in acute uncomplicated falciparum malaria.

Signed at Vienna, Austria

this Seventeenth day of December 1994

Walter Helmut Wernsdorfer